

REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

In response to the Restriction Requirement in the previous Office Action, Applicants elect Group I, claims 30-33, 38 and 41.

Claims 30-41 were pending in this application when last examined. Claims 34-37 and 39-40 were withdrawn as non-elected subject matter. Claim 30 is amended and claims 42-45 are newly added.

In the Amendment, Applicants added the limitation “formation of an amyloid plaque in a central nervous system is suppressed” into claim 30. The basis for this amendment is found on page 3, lines 25 to 26. Further, Applicants added new claims 42 to 45. New claim 42 is based on page 3, lines 26 to 29 of the specification. New claim 43 is based on page 3, lines 22 to 24 of the specification. New claim 44 is based on page 3, lines 29 to 32 of the specification. New claim 45 is based on page 9, lines 10 to 14 of the specification.

Thus, no new matter is added.

On pages 5-16, claims 20-33, 38 and 41 were rejected under 35 U.S.C. §103(a) as obvious over Huston et al. (US 2005/0255113) in view of Kuwako et al., Wyss-Coray et al., Milton et al. and Findeis et al.

As shown in claim 30, the claimed invention is directed to a method for treating Alzheimer's disease, comprising administering an adeno-associated virus vector in a therapeutically effective amount to a subject to suppress a formation of an amyloid plaque in a central nervous system and reduce a concentration of TGF- β in a blood of the subject, wherein the vector comprises DNA encoding a β -amyloid (hereinafter “A β ”) peptide and DNA encoding a signal peptide capable of extracellularly secreting said A β peptide, in an operative form.

The adeno-associated virus vector of the present invention comprising DNA encoding A β peptide together with the DNA encoding a signal peptide ensures secretion of the A β peptide so as to efficiently express the A β peptide as an antigen outside an infected cell (see, page 6, lines 1 to 5).

By administering such an adeno-associated vector to a subject, amyloid plaques such as senile plaques in the central nervous system are reduced (see, page 3, lines 22 to 26, page 5,

lines 32 to 36, page 14, line 5 to page 15 line 17, Table 1, page 16 line 14 to page 18, line 1, and elsewhere of the specification).

Moreover, by administering the claimed adeno-associated vector, the concentration of TGF- β in the blood is also reduced (see page 3, lines 26 to 27, and page 18, lines 2 to 19). It was previously known that TGF- β promotes pathological changes such as deposition of A β in blood vessels associated with cerebrovascular amyloid deposition and microvascular degeneration (see page 2, lines 21 to 29). However in the present invention, the concentration of TGF- β in the blood is also reduced so that A β deposition in the blood vessel associated with cerebrovascular amyloid deposition and microvascular degeneration is also suppressed (see page 3, lines 27 to 29).

Both amyloid plaques in the central nervous system and A β deposition in the blood vessel are pathologies of Alzheimer's disease and the simultaneous suppression of these pathologies is advantageous in the treatment of Alzheimer's disease. These technical features of the claimed invention are remarkable advantages for the treatment of Alzheimer's disease.

On the other hand, Wyss-Coray et al. discloses that a modest increase in TGF- β 1 production in transgenic mice expressing the human A β precursor protein results in a threefold reduction in the number of parenchymal amyloid plaques, and a 50% reduction in the overall A β load in the hippocampus and neocortex (see, Abstract lines 4 to 7 of Wyss-Coray et al.). That is, Wyss-Coray et al. discloses that the formation of amyloid plaques in the central nervous system is suppressed when the TGF- β level in the transgenic mice is increased. This feature is contradictory to the technical feature of the present invention in that "a formation of amyloid plaques in a central nervous system is suppressed and a concentration of TGF- β in a blood is reduced."

Further, Wyss-Coray et al. discloses that there is a significant inverse correlation between the formulation of amyloid plaques in the central nervous system and A β deposition in blood vessels in hAPP/ TGF- β 1 mice (see, page 614, right column, lines 15 to 20 & lines 24 to 25; page 614, right column, line 31 to page 615 left column, line 2; page 615, left column, lines 6 to 8; page 615, right column line 14 to page 616, line 2; page 616, left column, lines 43 to 46; page 616, right column, lines 14 to 16 & lines 34 to 36). This feature is also contradictory to the technical feature of the present invention that both the formulation of amyloid plaques in the central nervous system and A β deposition in blood vessels are suppressed.

As explained above, Wyss-Coray et al. discloses features contradictory to the technical features of the present invention that the formation of amyloid plaques in the central nervous system is suppressed, and the concentration of TGF- β in the blood is reduced, and then A β deposition in the blood vessel is suppressed. Thus, it is apparent that Wyss-Coray et al. teaches those skilled in the art away from the present invention. As such, Wyss-Coray et al. is precluded from use as a reference alone and in combination with other references. *See M.P.E.P. 2145(D)(2).*

Huston et al. (US 2005/0255113) discloses the immunization of a subject with a DNA vaccine such as an adeno-associated vector encoding a polypeptide comprising an epitope of an amyloid precursor protein (APP), which provokes a host antibody immune response sufficient to inhibit the formation of intracellular aggregates of the polypeptide.

However, Huston et al. fails to disclose or suggest an adeno-associated virus vector comprising DNA encoding A β peptide itself and DNA encoding a signal peptide. Thus, APP secreted by the DNA vaccine of Huston et al. is a different antigen from the A β peptide itself. APP generates A β peptide when partially decomposed by enzymes in neural cells (see paragraph 0002, lines 6 to 8 of the present specification). Without the decomposition in the cells, APP does not have the same antigenicity as A β peptide itself. According to the DNA vaccine of Huston et al., APP would be directly secreted outside cells without decomposition since APP comprises a signal peptide. Thus, it is apparent that the DNA vaccine of Huston et al. directly secreting APP outside the cells does not have the same antigenicity as the vector of the present invention which secretes A β peptide.

Further, Huston et al. fails to disclose or suggest that when administering the vector of the present invention to a subject, the formation of amyloid plaques in the central nervous system is suppressed and the concentration of TGF- β in the blood is reduced, and then A β deposition in the blood vessel is suppressed.

Kuwako et al. (Mol. Brain Res.107(2):167-75,2002) discloses the construction of adenovirus vectors expressing APP and APPA A β 20.

However, Kuwako et al. fails to disclose or suggest an adeno-associated virus vector comprising DNA encoding A β peptide itself and DNA encoding a signal peptide. Further, Kuwako et al. fails to disclose or suggest that when administering the vector of the present invention to a subject, the formulation of amyloid plaques in the central nervous system is

suppressed and the concentration of TGF- β in the blood is reduced, and then A β deposition in the blood vessel is suppressed.

Milton et al. (WO 2002/36614) discloses an antisense sequence of A β peptide residues 1-43 and fragment capable of binding to A β peptide (see claim 1).

However, Milton et al. fails to disclose or suggest an adeno-associated virus vector comprising DNA encoding A β peptide itself and DNA encoding a signal peptide.

Further, Milton et al. fails to disclose or suggest that when administering the vector of the present invention to a subject, the formulation of amyloid plaques in the central nervous system is suppressed and the concentration of TGF- β in the blood is reduced, and then A β deposition in the blood vessel is suppressed.

Findeis et al. (US Patent 5,854,204) discloses A β peptide 1-43 derivatives and sequences thereof (see column 64, Tables). However, Findeis et al. fails to disclose or suggest an adeno associated virus vector comprising DNA encoding A β peptide itself and DNA encoding a signal peptide. Further, Findeis et al. fails to disclose or suggest that when administering the vector of the present invention to a subject, the formulation of amyloid plaques in the central nervous system is suppressed and the concentration of TGF- β in the blood is reduced, and then A β deposition in the blood vessel is suppressed.

As mentioned above, none of the cited documents taken alone or in any combination disclose or suggest the adeno-associated virus vector of the present invention comprising DNA encoding A β peptide itself and DNA encoding a signal peptide as well as the technical feature of the present invention, i.e., the formulation of amyloid plaques in the central nervous system is suppressed and the concentration of TGF- β in the blood is reduced, and then A β deposition in the blood vessel is suppressed. Thus, those skilled in the art would not have arrived at the method of the present invention on the basis of the cited documents and there is no reason to combine these references at least because Wyss-Coray et al. teaches away from any such combination.

In addition, the present invention has advantageous technical features in relation to the treatment of Alzheimer's disease. According to the present invention, as claimed in claims 43 to 45, the therapeutic effects last more than 6 months with only a single dose and side effects such as cellular immune responses causing encephalitis are not substantially induced (see, new claims 43 to 45, paragraph 0012, Tests 2 and 5 and Figs. 1 and 3).

At the priority date of the present application, it was reported that when the A β peptide (AN1792) is administered to a subject as a vaccine in a clinical test, serious side effects such as cellular immune responses causing encephalitis were observed (see, *Neurology* 61: 46-54, 2003, page 46, Abstract [Attachment A]).

However, according to the present invention, as claimed in claims 43 to 45, by administering the vector of the present invention, therapeutic effects lasting more than 6 months can be achieved with a single dose while side effects such as cellular immune responses causing encephalitis are not substantially induced. In view of the disclosure of *Neurology* 61: 46-54, 2003, it is clear that the technical features of the present invention as claimed in claims 43 to 45 are remarkable and long sought features for the treatment or prevention of Alzheimer's disease. Thus, such features confirm that the present invention is not obvious as there is a long felt and unmet need for the claimed invention.

On the other hand, Wyss-Coray et al., Huston et al., Kuwako et al., Milton et al. and Findeis et al. alone and in combination fail to disclose or suggest the technical features of the present invention as claimed in claims 43 to 45, i.e., therapeutic effects lasting more than 6 months with only a single dose and side effects such as cellular immune responses causing encephalitis are not substantially induced.

Thus, the present invention is not obvious in view of Wyss-Coray et al., Huston et al., Kuwako et al., Milton et al. and Findeis et al.

Finally, Applicants again note that the present invention has led to ALZHEIMER'S DISEASE AWARD, 2005 presented by the Journal of Alzheimer's disease (see http://www.jalz.com/award/award_2005.html) [Attachment B]. Further, the present invention was introduced in the newspaper attached hereto as a promising candidate for the treatment or prevention of Alzheimer's disease [Attachment C].

These facts reflect that one skilled in the art considers the present invention unexpected and remarkable.

Thus, for the above-noted reasons, this rejection is untenable and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

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